EDITORIAL

OXYGEN-OZONE THERAPY AS ADJUVANT IN THE CURRENT EMERGENCY IN SARS-COV-2 INFECTION: A CLINICAL STUDY

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List of participating Centers in Appendix II

The aim of the multicentre study promoted by Nuova FIO is to evaluate the beneficial effects of the systemic Oxygen-Ozone (O2O3) therapy in patients suffering from SARS COV–2 disease in the early phases of the disease, before worsening, up to the need of tracheal intubation. The study is based on the rationale on that the systemic oxygen-ozone treatment could be effective, positively influencing the disease evolution and/or being able to mitigate the onset of the cytokine storm syndrome at least partially.

GENERAL INFORMATION

In these times of emergency for the pandemic of SARS-CoV-2 many treatment solutions are under investigation (1). Within this scenario, the oxygen-ozone mixture, which has shown to improve oxygen transport, but above all, has revealed a powerful anti-oedema, anti-inflammatory, and immune-regulatory activity, could represent a useful integration to other treatment strategies (2). The immune-regulatory effect can be ascribed to the anti-inflammatory activity, which is expressed through the release of cytokines with immune-stimulating and immunosuppressant power in an equal balanced equilibrium (2-5). Currently, in some cases of SARS-CoV-2 infection, an excessive release of cytokines (cytokine storm) seems to occur, especially IL-6 (5, 6). This may determine an exaggerated immune response, with detrimental effects on various organs and systems and possible onset an Acute Respiratory Distress Syndrome (ARDS) and Multi-Organ Failure (MOF). Systemic oxygen-ozone therapy could usefully interfere with this pathological mechanism (2- 5).

The therapeutic use of ozone (6-8) involves various possible methods of administration: local, intravenous, and rectal systemic, infiltrative (9-11). For patients hospitalized for CoViD-19, only the intravenous systemic pathway will be examined (12-15) (Table I). This approach will be implemented through the ozonization of a predetermined quantity of blood, in plastic or glass bags (disposable certified medical devices) suitable for use in this procedure, and subsequent re-entry of the ozonized blood into the

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patient's venous circulation. This procedure is not part of the transfusion procedures because the sampling and the re-introduction into the circulation takes place always using the same venous access, without detachment of the bag either during the sampling or during the re-infusion phase. In addition, the quantity collected does not exceed 200 ml and no blood storage takes place (Good clinical practices of the NuovaFIO scientific society www.lineeguidaozono.it).

RATIONALE IN THE USE OF OZONE FOR THE CURRENT HEALTH SITUATION

The oxygen-ozone systemic intravenous administration improves the oxygen transport capacity in the body, exerts an anti-oedema action (which is expected to counteract oedema lesions) useful to improve respiratory function. The typical anti-inflammatory and immune-modulating action of the mixture could prove invaluable in improving the body's response to the virus, especially in light of the most recent evidence which relates the worsening of the clinical picture to the host's response.

In association with this therapy, the administration of antioxidants will be allowed in order to reconstitute the substrate for the therapeutic action of ozone. The administration of antioxidants (16, 17) and the dosage should be recorded in detail for each single case treated.

In consideration of the negligible risks and the potential benefit, it seems possibly useful to propose this treatment for a structured verification.

STUDY DESIGN

The study is controlled, international, multicentre, conducted in open, with a control group represented by patients with equivalent initial characteristics, but treated only with the drug therapy deemed appropriate, without oxygen-ozone. Control group data will be collected retrospectively or prospectively. The controls will be grouped in homogeneous clusters matching with the cases treated, based on the parameters of severity, age, gender, and co-morbidity.

The treatment is proposed as compassionate (adjuvant treatment) and always in association with the therapies which in any case will be identified as the most suitable for the patient's benefit. It is believed that a week of continuous treatment may be a useful period to verify the effects, as emerged from the pilot study carried out at the Misericordia hospital in Udine (March 2020, unpublished data). The study will be conducted in compliance with the regulatory rules in force in Italy, the Good Clinical Practices ICH and the Good Clinical Practices established by the "Nuova FIO" Scientific Society.

MATERIALS AND METHODS FOR OXYGEN-OZONE THERAPY TRIAL

1. Systemic intravenous treatment with oxygen-ozone therapy takes place through the collection of venous blood.
2. The volume of blood drawn will be equal to 1.5g/Kg body weight.
3. The blood is collected in a bag or in a bottle containing citrate, CE marked and having the characteristics that are intended exclusively for use for oxygen-ozone therapy.
4. The volume of blood collected is immediately mixed with a gaseous volume of oxygen/ozone at a concentration of 30 mcg/ml.
5. The blood/gas mixture ratio must be 1/1 (for example: 100 ml blood/100 ml oxygen-ozone).
6. The reinfusion of the blood added with the oxygen ozone gas mixture must be immediate.
7. Posology of Treatment: once every 24 hours.
8. Duration of treatment: seven days.
9. For further technical details, please refer to the New FIO 2019 document "Guidelines and Good Clinical Practices" (available on the web at www.lineeguidaozono.it).

MONITORING OF THE EFFECTIVENESS AND OBJECTIVES OF THE STUDY

Objective: To compare the clinical progression of patients treated with O2-O3 to that of the control group.

Monitoring parameters

NEWS Score (National Early Warning Score) (20) G.R .; G.B .; Platelets; LDH, D-Dimer; PCR; IL6;

AST; ALT; PT Ratio.

FiO 2; PaO 2; Paco 2; Ph; VES; lactate; procalcitonin; Troponin-1; Ferritin.

PRIMARY ENDPOINTS:

Clinical progression:

a) Variation of the NEWS Score
b) Recourse to NIV
c) need for assisted ventilation by tracheal intubation
d) Onset of MOF
e) Mortality
f) Variation of the P-F RATIO (the minimum variation of 30% is considered positive outcome)
g) Variation of PaO2 in ambient air

SECONDARY ENDPOINTS:

a) Duration of subcritical conditions expressed by NEWS Score
b) Variation of IL-6
c) Variation of the ancillary laboratory data indicated above

SELECTION OF PATIENTS

Not less than 200 cases will be recruited with sequential continuous access criteria. Patients with the following characteristics will be enrolled:

1. Moderate non-hypercapnic hypoxic respiratory failure not ventilated
2. Positive confirmed buffer for COVID 19
3. Disease severity: NEWS Score Medium.

INCLUSION CRITERIA:

1. Rhino-pharyngeal swab positive for Covid-19
2. Hospitalized Patients
3. Males or females aged between 18 and 80
4. Informed Consent Signed
5. Chest CT scan with third stage changes (25% infiltrates)
6. PAO2 ≥ of 65 mmHg
7. Women of childbearing age with a negative test result prior to enrolment or in menopause or sterilized for at least one year
8. Disease severity level corresponding to the AVERAGE NEWS (National Early Warning Score) (18,

The NEWS score (18) provides 3 clinical alert levels:

- LOW: score 0: check every 12h; score from 1 to 4: check between 4-6h;
- MEDIUM: score from 5 to 6; score of 3 for a single parameter: check every hour
- HIGH: score ≥7: continuous monitoring and resuscitation advice.

Appendix I - NEWS 2 Score (National Early Warning Score) (18)

A rapid alert score (EWS) is a standardized guide for quickly determining a patient's degree of clinical severity and the timeliness and appropriateness of intervention. NEWS2 is the latest version of the National Early Warning Score (NEWS), which supports a system for standardizing the assessment and response to acute diseases. It is based on six measurements of physiological parameters: respiratory rate, oxygen saturation, body temperature; systolic pressure; heart rate; state of consciousness. Each parameter is graduated in levels, each of which is assigned a numerical value. The sum of the numerical values provides the measure of the deviation from normal physiology. The score is increased in cases where oxygen therapy is necessary (2 point increase). NEWS must not be used in children and adolescents ≤16 and in pregnant women: in these subjects the physiological response to acute states may, in fact, be different from that of the remaining patient population. Even the altered physiology of COPD patients can influence NEWS which must be corrected by clinical interpretation.

- The NEWS score provides 3 clinical alert levels:
- LOW: score 0: check every 12h; score from 1 to 4: check between 4-6h;
- MEDIUM: score from 5 to 6; score equal to 3 for a single parameter: check every hour
- HIGH: score ≥7: continuous monitoring and resuscitation advice.
- https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Fig. 1 *Summary table for NEWS scoring (18)*

EXCLUSION CRITERIA:

1. Full presence of MOF
2. Presence of known neoplasm in treatment or follow-up for less than 5 years
3. Platelets count <50,000 mm
4. Age <18 years or> 80 years
5. G6PDH deficiency (favism) or ongoing thyroiditis
6. Women with proven pregnancy or who do not use effective contraception methods
7. Patients with coagulopathies
8. Patients with angina or myocardial infarction in the 12 months prior to potential recruitment
9. HIGH NEWS Score
10. History of drug abuse or use of illegal drugs: use of soft drugs, e.g. marijuana within 6 months from screening or hard drugs, e.g. cocaine, amphetamine, phencyclidine within 1 year of screening
11. Alcohol abuse, i.e. regular use of more than 2 units of alcohol per day or 10 units per week or medical history of alcoholism (one unit of alcohol is equal to 250 ml of beer, 125 ml of wine or 25 ml of alcohol) or alcoholics recovered
12. Patient with a history of serious psychiatric disorders
13. Expected poor patient compliance
14. Previous participation in this clinical study
15. Participation in another clinical trial at the same time or in the previous 180 days (calculated from the date of the final exam of the previous study).

EVALUATION CRITERIA

The duration of the treatment will be equal to 7 (±1) days. The systemic Oxygen-Ozone treatment in the study can be stopped at any time by the end of the 7-day treatment period, in the event of symptom resolution or for safety reasons. Patients will be

followed for a total study duration of 14 (±2) days, with a period of 7 (±1) days treatment.

Each patient will be evaluated at the following time intervals:

T0, T + 24 hours, T + 48 hours, T + 72 hours, T + 96 hours, T + 120 hours, T + 144 hours, T + 168 hours, T + 14 days

Clinical data will be collected daily for 7 days of treatment and, 7 (± 2) days after the end of therapy, when a clinical check will be carried out in the hospitalization department or by remote telephone to establish the disease evolution during follow up.

At the above time intervals and in particular at T 0 (baseline) and T + 168 hours, the following items will be evaluated:

CBC with formula, Blood gas analysis, Ferritin, LDH, D-Dimer, Creatinine, AST, ALT, IL-6, PCR, GT range, VES, Albumin, Cholesterol, PT Ratio, Troponin, Pro-calcitonin, Lactate, Serum electrolytes, T lymphocyte subpopulations, NEWS Score.

Expected duration of treatment and daily observation of the patients enrolled in the study: 7 days (the administration of O2-O3 every 24 h starting from time T + 24) plus follow-up visit after 14 days. The patient's clinical evaluation will last until the systemic oxygen and ozone treatment is discontinued and a follow-up visit will be performed on day +14, 7 days after the last O2-O3 therapy.

SAFETY ASSESSMENT

The safety assessment will be based on the results of the blood chemistry tests already foreseen and mentioned among the rating criteria. Any adverse events will be recorded and reported, with a cause-and-effect assessment by the medical investigator. All concomitant disease and concomitant medication will be recorded.

STATISTICAL EVALUATION

Being a pilot study, never previously carried out on

Table I. *Clinical study procedures summary flow-chart*

Visit	TO	T+24H	T+48H	T+72H	7+96H	T+120H	T+144H	T+168		T+14days Telephone follow-up
Day	Day 1 Screening Start of therapy							Day 8(± 1) End of treatment, 7 (± 1) days after start of therapy		Day 14 (±2) Final visit 7 (±2) days after start of therapy
Informed consent	X									
Demographics	X									
Medical history and concomitant diseases	X	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)	X(1)		X(1)
Concomitant treatments	X	X(2)	X(2)	X(2)	X(2)	X(2)	X(2)	X(2)		X(2)
Lifestyle / Habits	X									
Physical exam	X	X								
Vital signs measurement	X	X								
Pregnancy test and contraception control (if woman potentially fertile)	X									
Protocol blood test	X	X	X	X	X	X	X	X		X
Inclusion / Exclusion criteria	X									
02-03 Administration to the patient	X	X	X	X	X	X	X			
Efficacy assessment by the investigator		X	X	X	X	X	X	X		
Total evaluation of efficacy by the patient		X								X(9)
Evaluation of tolerability by the investigator		X	X	X	X	X	X	X		
Adverse events reporting		X	X	X	X	X	X	X		X

(1) From Visit 2 to Visit T + 14 days, concomitant diseases changes will be reported

(2) From Visit 2 and Visit T + 14 days, concomitant treatments changes will be reported

(3) At Visit 1, information on consumption of alcohol, nicotine (including all nicotine-containing products), the history of drug abuse or use of illegal drugs will be collected

this type of pathology, the sample size (no ≥ 200) was calculated arbitrarily, in the hypothesis of collecting a sufficient number of patients representative to be able to draw reliable conclusions on the possible benefit the investigational treatment could bring to patients with COVID-19 infection.

Each participating centre will provide a series of at least 10 patients treated with Ozone according to the protocol and an equivalent number of patients treated with standard therapy, matching the 10 patients treated with ozone in terms of severity, range of age, gender, concomitant diseases and concomitant treatments.

Primary Endpoints:

1. Variation of the NEWS Score
2. Recourse to NIV
3. need for assisted ventilation by tracheal intubation
4. Onset of MOF
5. Mortality
6. Variation of the P-F RATIO (the minimum variation of 30% is considered positive outcome)
7. Variation of PaO2 in ambient air.
8. Secondary endpoints:
9. Duration of subcritical conditions expressed by NEWS Score
10. Variation of IL-6
11. Variation of ancillary laboratory data

ETHICAL CONSIDERATIONS: INFORMED CONSENT FORM

A dedicated informed consent form will be used and approved by the Ethics Committee.

Each patient will be described in detail and explained the rationale of the study, the advantages and the risks that this entails and each patient, after declaring full understanding and clearing up any doubts, will put his signature accompanied by date and time on the consent form, together with that of the proposer healthcare professional (Appendix III-IV).

Each patient will also receive a consent form for the processing of sensitive data, which however, will be anonymized during the collection and statistical processing. In compliance with the rules in force regarding sensitive personal data and rules governing clinical studies, the staff dedicated to monitoring and verification of the data collected, regulatory authorities and representatives of the Ethics Committee will have right of access to original data (Appendix V-VI). To this end, each participating clinical center will be assigned a 2-digit progressive number (01, 02, 03 ...) and after a dash, each patient recruited in the study will be attributed a progressive number, starting from 001, 002, 003. So, for example, the first patient enrolled from center 01 will be marked with the number 01-001.

CONCLUSIONS

The study will be carried out in different qualified centres treating COVID–19. The effect of the systemic administration of Oxygen Ozone will be evaluated in terms of both survival and progression of the disease compared with a control group. The outcome of this trial will enable to ascertain if oxygen-ozone therapy may effectively contribute to the fight against SARS-CoVID-19.

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Appendix II - LIST OF CENTERS ADHERING TO THE NUOVA FIO PROTOCOL

1. Ospedale di Piacenza, Dr. Micheli
2. Ospedale Bassini Milano, Dr. Gentile
3. Ospedale Fatebenefratelli Erba (CO), Dr. Donato
4. Ospedale SS. Trinità Hospital - ASSL Cagliari, Dr. Marcia
5. Azienda Ospedaliera Universitaria Careggi (FI), Dr. Pellicanò
6. ASL Salerno Presidio Ospedaliera Vallo della Lucania (SA), Dr. Giuliani
7. ASP 7 Ragusa, Dr. Bentivegna
8. ICS Maugeri Pavia, Dr. Miotti
9. Ospedale di Rovereto, Dr. Pedrotti
10. Policlinico Universitario degli Studi di Bari, Dr. Campobasso
11. Ospedale Riuniti di Ancona, Dr. Bernardini
12. Ospedale San Luca di Lucca, Dr. Cellai
13. Ospedale San Giuseppe Empoli, Dr. Vanni
14. Ospedale Cotugno Napoli, Dr Parrella
15. Asst Valle Olona Busto Arsizio Varese, Dr Gottardello
16. Ministero della Salute Slovacchia, Dr. Vjlitelka
17. Saudi German Hospital Dubai, Dr. Piracci
18. Victor Babes Hospital, Timisoara, Romania, Dr. Tiron
19. Victor Babes Hospital, Bucarest, Romania, Dr. Tiron
20. Ospedale San Pietro Fatebenefratelli, Roma, Dr. Martinelli

Appendix III - Informed consent to health treatment with OXYGEN-OZONE

(it consists of two pages)

LAW 22 December 2017, n. 219 - Art.1 - Paragraph 3. Each person has the right to know their own health conditions and to be informed in a complete, updated and comprehensible way regarding the diagnosis, prognosis, benefits and risks of diagnostic tests and the proposed health treatments, as well as regarding the possible alternatives and the consequences of any refusal of the health treatment and diagnostic assessment or of the renunciation of the same. Patient can refuse in whole or in part to receive the information or indicate the family members or a trusted person in charge of receiving it and to express consent in his place if the patient so wishes. The refusal or renunciation of information by a person in charge is recorded in the medical

record and in the electronic health record.

Paragraph 4. The informed consent, acquired in the ways and with the tools most appropriate to the patient's condition, is documented in writing or through video recordings or, for the person with disabilities, through devices that allow them to communicate. Informed consent, in any form expressed, is included in the medical record and in the electronic health record.

Paragraph 5. Every person capable of acting has the right to refuse, in whole or in part, with the same forms as in paragraph 4, any diagnostic assessment or health treatment proposed by the doctor for his pathology or individual acts of the treatment itself. It also has the right to withdraw at any time, with the same forms as in paragraph 4, the consent given, including any indication when the withdrawal involves the interruption of the treatment.

I subscribed ……..……
Born in ……..……
on…….....…….....….

INFORMATION

I have been informed by Dr. .... to be affected by: COVID-19 I agree to be subjected to SYSTEMIC OZONE OXYGEN therapy and I declare that the signature on this form confirms the information path I had with the health professionals who will treat me, in a longer and more complete explanation than what is summarized here for brevity. I therefore declare that I have been informed verbally on the diagnosis of the disease from which I am affected, on its therapeutic indications, on the treatment to which I will be subjected. I am aware that the volumetric doses and the oxygen-ozone concentrations and the sequence of operations established by the Oxygen-Ozone Therapy Guidelines will be used (published and updated on the website ww.lineeguidaozono.it) considered the safest possible at the current state of knowledge. I am aware that systemic ozone administration is contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency "Favismo". Although there are no scientific studies that contraindicate their use (on the contrary, positive experiences of oxygen ozone therapy for the treatment of some pathologies related to pregnancy are reported).

I'm are aware of the possible adverse or side effects, i.e. TRANSITORY TACHYCARDIA, TRANSITIONAL LOCAL PAIN, PHLEBOPATHIES, INFECTIONS, ECCHYMOSIS AND HAEMATOMAS IN INOCULATION, VAGAL REACTIONS and what are the currently known percentages of each reported effect.

Appendix IV – CONSENT

In conclusion, after receiving the requested clarifications, I sign this document and, knowing that with the signing of the parties, the deed acquires the value of the acceptance of my informed consent and of attestation of the facts reported therein, I specifically declare:

A) to be aware that I can withdraw my consent at any time;
B) to have understood what the healthcare professional has explained and clarified, as summarized above;
C) to have discussed the details of the treatment with Dr. ..... solving all my doubts;
D) to accept the risks of therapy that have been explained to me;
E) I ask to proceed with the treatment itself;
F) consent to the execution of the oxygen-ozone therapy treatment;
G) any additional notes to be crossed where not necessary.

I authorize the physician, where necessary, to vary the planned intervention, this in order to achieve the best therapeutic effect, or in order to deal with any pathological states that are presently not yet evident.

I am aware that I can withdraw my consent at any time during the therapeutic process.

I have been informed of the potential and operational limits of the health facility in which I am hosted, as well as of the possibility of performing this therapy in other structures. I have clear that any further doubt or curiosity that could arise later, will be satisfied by the same physicians.

Place…….....…….
Date …….....…….
Signature of the doctor who informed the patient
…….....

Place .....…….
Date …….....…….
Patient signature …….....
(signature and date must both be signed by the patient)

Appendix V - INFORMATION ON PERSONAL DATA pursuant to art.13 of the European Regulation 2016/679 (GDPR ")

HOLDERS and PURPOSE OF THE PROCESSING

The Data Controllers of the personal data referred to or referable to it processed during the clinical study by the Title "Use of ozone as an adjuvant in the current emergency from SARS VOC 2 infection", (the "Study") are:

The promoter _____

The Center_____

Each of the Data Controllers will independently process their data and, in particular, the data related to your health (the "Data") as necessary in relation to the objective of the Study and in accordance with the provisions of GDPR, by Legislative Decree 30 June 2003 n. 196 (Italy), by the rules of good clinical practice (Legislative Decree June 24, 2003 n. 211) and as described below. The acquisition, processing, use and storage of data are indispensable for carrying out the Study; any refusal will not allow your participation in the Study.

CODING

After obtaining your personal data, the doctors who will follow you during the Study, and their collaborators, will identify you with a code (the "Code"). With the exception of your name, all the Data that will be collected or used during the Study (including date of birth, gender, weight, stature and clinical data inherent to your state of health) will be recorded, processed and stored by marking them with the Code (of below, these data will be referred to as the "Coded Data"). No personal identification (name, initials, date of birth or other data) will be included in the Coded Data. For the entire duration of the Study, your personal data may be consulted from time to time only by specifically appointed persons and for checking that the encoded data have been correctly reported from the paper files and databases of your study doctor.

PROCESSING METHODS AND COMMUNICATION OF DATA TO THIRD PARTIES

The Data will be collected, used, processed and stored both in paper and electronic format. During of the Study or after its conclusion will have access to your personal data:

• the owner's staff and the members of the Ethics Committee;

• health and control authorities;

• the investigating doctors, the person in charge of monitoring and verifying the study management methods.

Your data will not be disclosed or made available to the public. The Coded Data will be published only keeping its strictly in anonymous form at congresses and scientific conferences or through scientific or statistical publications.

HOW THE CODED DATA WILL BE USED?

The Coded Data will be used for the purposes of the Study as well as during or for the purpose of communications with competent authorities in the health sector or in other sectors;

• to support the planning of future studies;

• research compatible with the outcome of this study, including statistical purposes.

Occasionally, the Coded Data may be exported to countries that may have less standards data protection laws in force in Italy or in the European Union. Any transfer will be carried out in the manner provided for in articles 44 and following of the GDPR.

HOW LONG WILL YOUR DATA BE STORED?

The documents and records containing the Data will be kept for the maximum retention period required or permitted by local regulations.

WHAT RIGHTS DO YOU HAVE ON YOUR PERSONAL DATA?

Access rights, cancellation, limitation and portability. The interested parties are recognized the rights referred to in art. from 15 to 20 of the GDPR.

By way of example, each interested party may therefore:

• obtain confirmation that personal data processing is being processed;

• if a treatment is in progress, obtain access to personal data and information relating to processing and requesting a copy of personal data;

• obtain the correction of inaccurate personal data and the integration of incomplete personal data;

• obtain, if one of the conditions provided for by art. 17 of the GDPR, the cancellation of personal data concerning him;

• obtain, in the cases provided for by art. 18 of the GDPR, the limitation of the treatment;

• receive personal data concerning him in a structured format, commonly used and readable by automatic device and request their transmission to another holder, if

technically feasible. Right to opposition. Each interested party has the right to object at any time to the processing of his data personal data carried out for the pursuit of a legitimate interest of the Owners. In case of opposition, your personal data will no longer be processed, provided that there are no legitimate reasons for proceeding with the treatment that prevail over the interests, rights and freedoms of the interested party or for the assessment, exercise or defense of a right in court.

• Right to propose a complaint with the Guarantor. Each interested party may propose a complaint with the Guarantor for the Protection of Personal Data in the event that you believe that the rights you hold pursuant to GDPR, in the manner indicated on the Guarantor's website accessible at the address: www.garanteprivacy.it have been violated.

• For further information and communications during the study, you can contact the following staff:
Dr./Prof._____ Tel ._____

Appendix VI - CONSENT TO THE PROCESSING OF PERSONAL DATA

Having read the information above and having understood its contents, by signing this letter, I agree:
- to the processing of my personal data with the methods and purposes indicated above;
- to the possible transfer of my personal data outside the European Economic Area.

To be filled in manually by the patient

_____

_____

Name and surname of the patient in capital letters

_____

_____

Patient's signature and date
(signature and date must both be signed by the patient)

To be filled in manually by the doctor
I conducted the explanation of the protocol and the processing of personal data and I personally obtained the consent of the patient
Name and Surname of the Doctor in capital letters

_____

_____

Doctor's signature _____
Date _____